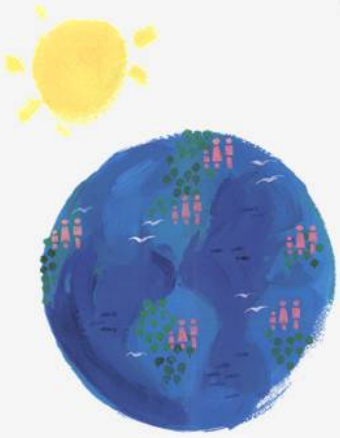
NICEATM

National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods

ICCVAM

Interagency Coordinating Committee on the Validation of Alternative Methods



Overview of the ICCVAM Workshop on Best Practices for Assessing the Potential for Chemically Induced Allergic Contact Dermatitis (ACD)

Joanna Matheson, Ph.D.

CPSC and ICCVAM Vice-chair

SACATM Meeting

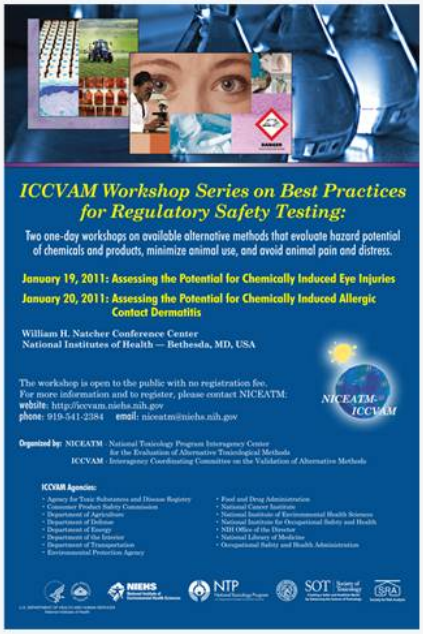
June 16, 2011

Hilton Arlington
Arlington, VA

National Toxicology Program

NIEHS

Best Practices for Regulatory Safety Testing: ACD Workshop



- NIH – William H. Natcher Center, Bethesda, MD
- January 20
- 77 participants
  - Mostly government and industry participants
  - Equal representation
- Poster session
  - 18 ACD posters

Pre-workshop Communications Efforts

- FR Notice (Oct. 13)
- Six announcements sent to ICCVAM email list (958 individuals)
  - Requests to "spread the word" also sent to 12 additional industry contacts not on ICCVAM email list
- Articles in regular NICEATM updates to NTP and ALTEX
- Requests to post on websites sent to 25 organizations
  - 15 actually confirmed posted
- Posters sent to EPA, CPSC, FDA via ICCVAM reps
- SOT and SRA co-sponsorship
  - Email announcement to full SOT membership
- Also supplementary emails to relevant SOT specialty sections

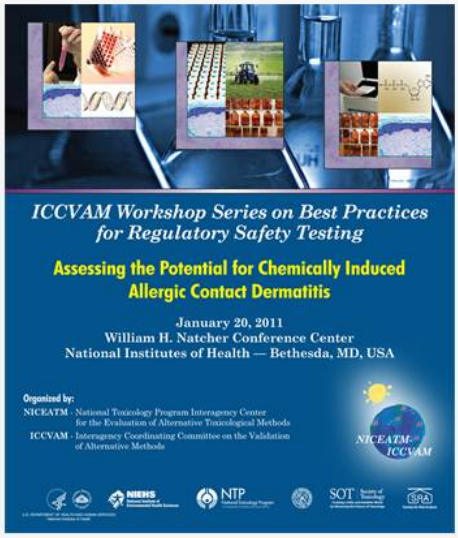
NIH Center for Information Technology Webcast

- Live webcast of workshop
  - Over 90 online viewers
- Webcast included all plenary sessions

- Archived webcast available at:
  - NIH videocast page: http://videocast.nih.gov/PastEvents.asp
  - NICEATM-ICCVAM website: http://iccvam.niehs.nih.gov/meetings/Implement-2011/ImplmtnWksp.htm

Summary of Program: ACD Workshop

- Introduction/Public Health Impact
- Available Test Methods
  - Reduced murine local lymph node assay (rLLNA)
  - LLNA: BrdU-ELISA
  - LLNA: DA
  - Direct Peptide Reactivity Assay (DPRA)
- U.S. Requirements for Consideration of Alternatives
- Regulatory Agency Roundtable Discussion
  - EPA
  - FDA
  - CPSC
  - OSHA
- Case Studies
  - Breakout groups
  - Summary presentations



ACD Safety Test Methods Discussed

- Traditional LLNA
  - Uses a radioactive marker to assess lymph node cell proliferation
  - Updated OECD Test Guideline 429 (July 2010)
- rLLNA
  - Uses 40% fewer animals
  - Updated OECD Test Guideline 429 (July 2010)
- LLNA: BrdU-ELISA
  - Uses bromodeoxyuridine (BrdU) measured by ELISA to assess lymph node cell proliferation
  - New OECD Test Guideline 442B (July 2010)
- LLNA: DA
  - Uses ATP by luciferin-luciferase assay to assess lymph node cell proliferation
  - New OECD Test Guideline 442A (July 2010)
- DPRA
  - Uses HPLC to monitor a chemical's potential to deplete a nucleophile-containing synthetic peptide
  - Currently undergoing prevalidation by ECVAM

New ACD Safety Test Methods in the Validation Pipeline

- DPRA (Procter & Gamble)
- Human Cell Line Activation Test (h-CLAT, Kao and Shiseido)
  - Uses flow cytometry to monitor induction of two protein markers on the surface of a human monocytic leukemia cell line following exposure to chemical
- Myeloid U937 Skin Sensitization Test (MUSST, L'Oréal)
  - Uses flow cytometry to monitor induction of a protein marker on the surface of a human monocytic cell line following exposure to chemical

Survey Responses: ACD Workshop

- Number of surveys received: 19
  - Total attendance: 77
- Respondents:

[1]Represents a summary of data from several questions

Case Studies Overview

- Three ACD case studies were presented to highlight:
  - The potential for reducing animal use by using the validated rLLNA
  - How to conduct and interpret results from the validated nonradioactive LLNA methods
    - LLNA: BrdU-ELISA
    - LLNA: DA

Case Study Summaries (1)

- Case study 1: Use of rLLNA
  - To test substances that are suspected to be nonsensitizers. Note that the rLLNA should also be used to test suspected sensitizers when dose-response information is not needed
  - Consideration and appropriate use of the rLLNA can decrease animal use by 40%
    - 80% of chemicals/products are nonsensitizers in standardized tests[1]
  - The use of a prescreen test to determine the dose to be tested in the rLLNA

[1]Safford RJ. 2008. Reg Tox Pharmacol 51: 195-200.

Case Study Summaries (2)

- Case study 2: Use of LLNA: DA
  - Illustrated dose selection for the LLNA: DA using prescreen data
- Case study 3: Use of the LLNA: BrdU-ELISA
  - Demonstrated how an outlier in the vehicle control group can produce erroneous results that may impact the classification of a substance using the LLNA: BrdU-ELISA
  - Emphasized the need to collect individual animal data in order to identify outliers that could yield false negative results

Acknowledgements

- Society of Toxicology (Co-sponsor)
- Society for Risk Analysis (Co-sponsor)
- ICCVAM
- ICCVAM Interagency Immunotoxicity Working Group
- NICEATM Staff

Questions for SACATM

- Based on the background materials provided, please provide comments on the extent that the workshops addressed the workshop goals, which were to:
  1. Provide an overview of the available methods in each area, including the applications, strengths and weaknesses of each method
  2. Provide information on the procedures for conducting and interpreting data in accordance with regulatory testing requirements and guidelines
  3. Allow an opportunity for participants to become familiar with data generated by each test method
  4. Provide a forum for scientists to share information on the appropriate use of results in regulatory safety testing
  5. Discuss challenges of incorporating alternative test methods into regulatory safety testing guidelines
- Do you have suggestions for enhancing the effectiveness of future workshops?
- How might NICEATM, ICCVAM, and ICCVAM member agencies increase participation in future implementation workshops and create greater awareness and consideration of available alternative methods?